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DATE MAILED: 4-26-95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1/23/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 3, 5-10, 17-19, 23-24, 28-32, 35, 37-42, 67-76 & 78 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 2, 4, 11-14, 16, 20-22, 25-27, 33, 34, 36, 43-66 & 77 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 3, 5-10, 17-19, 23-24, 28-32, 35, 37-42, 67-76 & 78 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. Claims 2, 4, 11-14, 16, 20-22, 25-27, 33, 34, 36, 43-66 and 77 have been cancelled in response to applicant's amendment.

16. Claims 1, 7-10, 17-19, 23, 24, 28-32, 35 and 37-42 have been amended.

17. Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, 67-76 and 78 are pending.

18. Claims 67-76 have been withdrawn as directed to a non-elected invention.

19. The rejection of claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility, has been withdrawn upon further consideration.

20. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention, i.e. for failing to provide an enabling disclosure.

A) Applicant has not disclosed to one of ordinary skill in the art how to practice the claimed invention without undue experimentation. There is a high degree of unpredictability associated with methods claimed for the following reasons:

Waldmann [Science 252:1657-1662 (1991)] teaches that effective therapy using monoclonal antibodies has been elusive and describes limitations of murine antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by in-vitro and animal model studies have not correlated well with in-vivo clinical trail results in patients. Further Harris et al. [TIBTECH 11:42-46 (1993)] state "there is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy", see page 42, column 2,

lines 3-7. Harris et al. also teach "the residual HAMA response to chimeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective", see page 42, column 3, lines 17-20. Applicant has only provide evidence of therapeutic use in nude mice, which are immunosuppressed. Nude mice therefore are not a sufficient model system to test anti-murine responses to antibodies. It is well known in the art that antibody-based therapies have very limited success. One of ordinary skill in the art would not readily accept that Applicant's claimed modified antibodies would be satisfactory for human therapy as asserted in the specification. As evidenced by Osband et al. [Immunotherapy 11(6):193-195 (1990)] one of ordinary skill in the art would not readily accept the utility of an immunotherapeutic agent without convincing objective evidence of efficacy in humans (see paragraph bridging pages 193-194). As further evidenced by Waldmann and Dillman [Ann. Internal Med. 111:592-603 (1989)] it is well known in the art that the use of monoclonal antibodies has, in general, only met with very limited success in humans. Waldmann teaches that immunotoxins have not lived up to expectations and that "the results of in vivo clinical trials in patients with cancer with first-generation immunotoxins did not fulfill the hopes engendered by in vitro and animal model studies" (see page 1660, second column, fourth full paragraph). Dillman teaches that "as a therapeutic modality, monoclonal antibodies are still promising but their general use will be delayed for several years" (see Abstract). In addition, Hird et al. [Genes and Cancer (1990) chapter 17] teaches that "the data obtained from mouse studies are useful, but cannot be directly translated to apply to the human situation" (see page 185, first full paragraph). Other factors such as proteolytic degradation, immunological inactivation, antigenic modulation or antigen shedding by the tumor, as well as factors influencing localization of the antibody such as the anatomical location of the tumor and its vascularity and blood flow, all have bearing on the efficacy of the antibody therapy. Further, with respect to immunotoxins, the level of antigen expression and the rate and route of internalization also effect the therapeutic efficacy of the antibody. Given the teachings of Osband et al., Waldmann, Dillman, Hird et al. and Harris et al. as well as the other well known factors effecting antibody therapies, one of ordinary skill in the art would not readily accept Applicant's claimed utility on its face, absent some showing of convincing objective evidence of therapeutic or diagnostic utility. Therefore, the claims are rejected as lacking patentable utility. Further, regarding proteins in general - there is a high degree of unpredictability associated with the use of proteins in vivo: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) the protein may otherwise not reach the target area because, for example, (a) the

protein may not be able to cross the mucosa, (b) the protein may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo use.

Applicant contends, citing Thorpe TibTech 11:40-43 (1993), that monoclonal antibodies are useful as therapeutic agents and in vivo diagnostic agents. Applicant is invited to consider, Harris et al. which follows the Thorpe citation in the same journal at pages 44-46, previously made of record. Harris et al. state "there is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy", see page 42, column 2, lines 3-7. Harris et al. also teach "the residual HAMA response to chimeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective", see page 42, column 3, lines 17-20. Clearly, there is reason to believe that there is a high level of unpredictability in the field, especially when evidenced by two conflicting reports from different meeting published in the same journal. Applicant suggests in response to the utility rejection, now withdrawn, that the burden of proof shifts to the applicant only if there is a reasonable doubt as to the truth of the applicant's assertions not just any doubt. The references already of record in addition to those presented by applicant provide overwhelming evidence that there is a high degree of unpredictability associated with the claimed invention. Applicant response to the Dillman, Hird and Osband references by stating that the claimed invention is not directed to cancer treatment. But, for the most part the general teachings presented in these references, regarding the application of antibodies, is applicable to any in vivo method. Applicant has provided Brusick, The role of animals in biomedical research [exhibit 3] and Rawlins. Long-Term Animal Studies: Their Predictive Value for Man [exhibit 4] arguing that in vitro studies demonstrate a reasonable correlation between in vitro and in vivo use. Brusick is addressing safety issues and is not concerned with whether the agent actually works or not. Rawlins, while also concerned with safety issues, expressly states that "the information provided by animal pharmacology tests is the most important part of preclinical program. . . ." [Page 18, last full paragraph]. Applicant states at page 11 of the response that they have taught that administration of the B7 antigen will result in effects similar to the use of anti-CD28 monoclonal antibodies reactive with the CD28 receptor in vivo. However, upon review of the specification applicant presents no objective evidence to support this allegation. In fact, there is no in vivo data presented in the specification. It remains unclear, give the extreme unpredictability of the agents of the claimed methods how such an allegation can be made with out substantiating evidence. The unpredictable nature of the agents involved in the claimed invention are such that a determination

must be made on a case by case basis. In this case a reasonable correlation between the in vitro results provided and in vivo use has not been provided. Applicant suggests that adoptive immunotherapy is encompassed by the claimed method. Applicant is invited to review Basse et al. [Cancer Immunol. Immunother. 34:221-227 (1992)]. Basse et al. teach that while adoptive immunotherapy has proven successful in many animal models the clinical studies have been less encouraging with response rates of 20% or more observed only for melanomas and renal cell carcinomas. The arguments related to the B7Ig and CD28Ig fusion proteins is not persuasive. In vitro studies do not account for the unpredictable nature of the in vivo environment. For example: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half life of the protein; (2) the protein may otherwise not reach the target area because, for example, (a) the protein may not be able to cross the mucosa, (b) the protein may be adsorbed or absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo use. Thus, applicant has failed to provide an adequate written description of the invention and failed to adequately teach how to use the invention. The specification does not enable a person of ordinary skill in the art to practice the claimed invention without undue experimentation. The breath of the claims is drawn to in vivo use. Even if it were drawn to in vitro use the specification alleges that such use would be for adoptive immunotherapy which is unpredictable. Applicant alleges that the in vitro data can be used to design in vivo protocols. However, this is inconsistent with Brenner v. Manson, 148 USPQ 689 (S.Ct. 1966). which requires that the claimed invention be in currently available form. Applicant's comments were considered but were not found persuasive. This objection still stands.

B) The disclosure provides only a description of B7 antigen on CHO cells. Other immobilized B7 sources have not been enabled by the specification for applicant's claimed invention. Applicant states that the disclosure provides more than a description of B7 antigen on CHO cells, but they will not address this issue further "since it is irrelevant because the claimed invention is not directed to using immobilized B7." Applicant is invited to consider claims 9 and 10. Applicant's comments were considered but were not found persuasive. This objection still stands.

C) The disclosure does not provide an enabling description of a method having the steps of reacting B-cells with T-cells. Applicant states this is "irrelevant since the claimed invention is not directed to reacting B-cells with T-cells." Applicant is invited to consider claim 17. Applicant's comments were considered but were not found persuasive. This objection

still stands.

D) The disclosure does not provide an enabling description of fusion proteins of at least a portion of the extracellular domain of the CD28 receptor. The disclosure is specifically directed to a fusion containing amino acid residues, of the CD28 receptor, from about position 1 to 134 and a second amino acid sequence corresponding to the hinge, CH2 and CH3 regions of human IgG-1 constant domains. Applicant argues that the examiners citation of a fusion protein containing amino acid residues from about position 1 to 134 and a second amino acid sequence corresponding to the hinge, CH2 and CH3 regions of human IgG-1 constant domains, supports the claim. However, the phrase "at least a portion of the extracellular domain of the CD28 receptor" reads on 1 amino acid. 1 amino acid clearly will not function in the claimed invention. Applicant's position is not persuasive. Applicant's comments were considered but were not found persuasive. This objection still stands.

E) Applicant's specification does not support a method of inhibiting T cell proliferation with any B7 antigen derivative. Specifically, B7 on CHO cells, or immobilized in any way will not result in a method of inhibiting. Instead, such a B7 derivative will cross-link the CD28 receptor resulting in T cell activation and increased proliferation. Additionally, the specification does not provide an enabling description of the use of an anti-CD2 antibody in a method of inhibiting T cell proliferation. Applicant misses the point - by stating the specification teaches B7Ig. The point was to have applicant limit the claimed invention limited to B7Ig. Additionally, applicant has not addressed the anti-CD2 antibody issue presented. Applicant's comments were considered but were not found persuasive. This objection still stands.

F) Applicant's specification does not support the scope of claims directed to a method for preventing the binding to the CD28 receptor to the B7 antigen. The specification discloses that a method of this type is use to inhibit functional T cell responses. However using a monoclonal antibody 9.3 to inhibit binding of B7 to CD28 will result in T cell activation and proliferation resulting in a functional T cell response. Applicant cites several sections of the specification, and then states that others, like Ledbetter et al. infra, showed that antibody 9.3 binds CD28 thereby resulting in T-cell activation and proliferation. This is the issue. The claims are drawn to a method of inhibiting T cell proliferation. Contacting T-cells results in T cell activation not inhibition. Thus, the 9.3 antibody represents an inoperative embodiment of the claimed invention, therefore it is requested that the claims be limited to exclude the 9.3 antibody. Applicant's comments were considered but were not found persuasive. This objection still stands.

G) It is unclear from the specification how the methods of claims 9, 10, 15, 17, 35 and 38 will result in inhibiting T cell proliferation. Note the deleted subject matter of claim 17, "T cell responses are stimulated". An anti-CD28 monoclonal antibody as that of claim 35 will cross-link the CD28 receptor resulting in activation of proliferation. This is why a Fab fragment such as that of claim 37 is necessary. Applicant takes the position that 112 first paragraph requires only that applicants teach how to make and use the claimed invention. That is what applicant has failed to do. The claims are drawn to a method of inhibiting T cell proliferation. An anti-CD28 antibody will stimulate T cell proliferation. Thus, applicant is invited to limit the claimed invention to exclude reference to an anti-CD28 antibody. Applicant's comments were considered but were not found persuasive. This objection still stands.

H) The specification does not enable a method of inhibiting proliferation using an intact antibody molecule to the CD28 receptor. At page 47 of the specification applicant states that the inhibitory effects of anti-CD28 mAb 9.3 on the MLR responses on T cells are consistent with previous observations reported by Damle et al., J. Immunol. 120:1753 (1988). Damle et al. teach the inhibitory effect of anti-CD28 mAb in the MLR was reversed by cross-linking of anti-CD28 mAb with anti-mouse κ mAb. Since applicant's invention is not limited to in vitro use it would be expected that the anti-CD28 mAb would be cross-linked in vitro thereby activating the T-cell. Applicant's comments were considered but were not found persuasive. This objection still stands.

I) The specification does not contemplate the CTLA-4 molecule. Thus even if the CD28/B7 interaction is inhibiting the CTLA-4/B7 interaction can still activate T cells. Applicant is encouraged to consider Linsley et al. [J. Exp. Med. 174:561-569 (1991)]. Applicant argues that the claimed invention is not directed to inhibiting T cell proliferation using all possible pathways. However, the objection to directed to the unpredictability of the claimed invention. Applicant suggests that T cell proliferation can be inhibited using a molecule which binds CD28. Since CTLA-4, a homologue, of CD28 is present on T cells it remains unclear if applicant can accomplish the inhibition claimed. CTLA-4 offers a second pathway for activation of T cells, thus even though the CD28/B7 interaction is prevented the CTLA-4/B7 interaction can result in activation of T cells irregardless of applicant's claimed method. Applicant's comments were considered but were not found persuasive. This objection still stands.

23. Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 are rejected under 35 U.S.C. § 112, first paragraph, for the

reasons set forth in the objection to the specification. This rejection still stands, for the reasons given above.

24. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25. The provisional rejection of claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 has been withdrawn in response to applicant's abandonment of the 08/076,071 application.

26. Claims 1, 3, 5-8, 18, 23, 24, 41 and 42 are rejected under 35 U.S.C. § 103 as being unpatentable over Linsley et al. [PNAS 87:5031-5035 (1990)] and Freeman et al. [J. Immunology 143:2714-1722 (1989)] in view of Capon et al. [WO 89/02922]. Briefly the claims are directed to a method of inhibiting T cell proliferation by blocking the interaction between the CD28 and B7 complex using the B7 antigen. Linsley et al. teach the interaction between CD28 and B7 is important in crosslinking CD28 and activating T cell proliferation, see entire paper. Linsley et al. do not teach a soluble B7 protein. Freeman et al. teach the sequence of the B7 molecule, figure 3, page 2717. Note that amino acid 217 begins the transmembrane portion of the molecule and amino acids 1-216 contain the extracellular portion of the molecule. Freeman et al. do not teach a B7Ig fusion. However, Capon et al. teach adhesion molecules fused to the constant domain of an immunoglobulin protein, see entire article. Capon teach that this stabilizes a solubilized receptor protein, increases plasma half life and improves therapeutic efficacy, see page 6, first full paragraph. The bridging paragraph of pages 9-10 teach functional domains of an adhesion protein is fused to the hinge, CH2 and CH3 domains of the constant region of an

immunoglobulin heavy chain. Thus, from the combined teachings of Freeman et al. with Capon et al. a soluble B7Ig fusion protein would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made. Linsley et al. add to the combination of Freeman et al. and Capon et al. providing motivation to a person of ordinary skill in the art to inhibit the interaction between B7 and CD28 to inhibit the proliferation of T cells. Therefore as a whole the claimed invention is prima facia obvious to a person of ordinary skill in the art at the time the invention was made.

Applicant contends that the parent applications 07/547,980 and 07/498,949 enable the claimed invention and therefore Lindsley et al. is not a valid reference. Applicant is invited to reconsider the parent applications listed above and point by page and line number to either, where support can be found for using the B7 antigen to inhibit T cell proliferation. Applicant states that the combination of Freeman et al. with Capon et al. is improper for a number of reasons. Essentially, that since CD4 and B7 do not share a common structure a Ig fusion protein would not be attainable. However, applicant is reminded that an obviousness rejection requires only a reasonable expectation of success. Capon et al. provides such an expectation by stating that adhesion molecules can be modified according to his method. B7 is an adhesion molecule which according to Linsley et al., which is a valid reference, binds CD28. A person of ordinary skill in the art would have produced the B7Ig fusion protein with a reasonable expectation of success to inhibit T cell activation, as taught by the combination of references. Applicant argues that there is no equivalent showing that the functional domains can be interchanged throughout the immunoglobulin superfamily, whose members vary widely in structure. Capon et al. teaches that "adhesions are cell surface polypeptides having an extracellular domain which is homologous to a member of the immunoglobulin gene superfamily." Applicant further states that "functional domains cannot be interchanged within the immunoglobulin superfamily without a loss in affinity and specificity, citing Linsley et al., J. Exp. Med. 173:721-730 (1991). It is unclear, where in this references applicant is citing from. In this reference Linsley et al., obtain a functional B7Ig fusion protein. It is not clear why applicant takes the position that the "functional domains cannot be interchanged within the immunoglobulin superfamily." Applicant states they were the first to discover that B7 recognizes and binds CD28 and CTLA4 antigens and therefore the prior art does not suggest making the combination of references used in this rejection. Further, applicant suggests that without motivation to

produce the B7Ig one is merely picking and choosing among the individual elements of assorted prior art references to recreate the claimed invention. To the contrary, the combination of references teach the interaction between B7 and CD28, in addition to teaching a method of inhibiting T cell activation. Further, the combination of references provide motivation to produce the B7Ig for use in such a method. Therefore, applicant's arguments are not persuasive. Applicant's comments concerning the absence of recognition that B7 binds CD28 are not persuasive in view of Linsley et al. who teaches this interaction. As a whole applicant's comments have been considered but were not found persuasive. Therefore this rejection still stands.

27. Claims 19 and 78 are rejected under 35 U.S.C. § 103 as being unpatentable over Linsley et al. [PNAS 87:5031-5035 (1990)] and Aruffo et al. [PNAS 84:8573-8577 (1987)] in view of Capon et al. [WO 89/02922]. Briefly the claims are directed to a method of inhibiting T cell proliferation by blocking the interaction between the CD28 and B7 complex using the CD28 receptor. Briefly the claims are directed to a method of inhibiting T cell proliferation by blocking the interaction between the CD28 and B7 complex using the B7 antigen. Linsley et al. teach the interaction between CD28 and B7 is important in crosslinking CD28 and activating T cell proliferation, see entire paper. Linsley et al. do not teach a soluble B7 protein. Aruffo et al. teach the sequence of the CD28 molecule, figure 2, page 8574. Aruffo et al. do not teach a CD28Ig fusion. However, Capon et al. teach adhesion molecules fused to the constant domain of an immunoglobulin protein, see entire article. Capon teach that this stabilizes a solubilized receptor protein, increases plasma half life and improves therapeutic efficacy, see page 6, first full paragraph. The bridging paragraph of pages 9-10 teach functional domains of an adhesion protein is fused to the hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain. Thus, from the combined teachings of Aruffo et al. with Capon et al. a soluble CD28Ig fusion protein would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made. Linsley et al. add to the combination of Aruffo et al. and Capon et al. providing motivation to a person of ordinary skill in the art to inhibit the interaction between B7 and CD28 to inhibit the proliferation of T cells. Therefore as a whole the claimed invention is prima facia obvious to a person of ordinary skill in the art at the time the invention was made.

Applicant makes the same type of arguments as were presented in the response to the previous rejection. For the same reasons this rejection still stands.

NEW GROUNDS FOR REJECTION

28. Claims 9, 10, 15 and 17 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant is invited to review the originally filed claims, then consider the specification. The claims listed in this rejection are vague and indefinite as applied to a method of inhibiting T-cell proliferation. The specification supports this position. Applicant is invited to amend the claims to specifically comply with the base claim presumption that the method is to inhibit T cell proliferation.

29. Claims 28-34 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 28-34 depend from cancelled claim 26, which depends from independent claim 19. Claims 28-34 are vague and indefinite in the recitation of "derivative." There is no antecedent basis for this word in either claim 19 or cancelled claim 26. Further the only suggestion of fragment in the claim is directed to the 9.3 antibody fragment and not to a portion of the extracellular domain of the CD28 receptor as claims 28-34 intend. The specification does not provide any guidance on this issue.

30. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

31. Claims 35 and 37-40 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ledbetter et al. [J.I. 135(4):2331-2335 (1985)]. Ledbetter et al. teach Fab fragments of anti-TP44(CD28) were ineffective in inducing T cell proliferation, see abstract. These antibody Fab fragments will inherently block the interaction between CD28 and B7. The Fab fragment is derived from monoclonal antibody 9.3. Applicant contends that since Ledbetter et al. teach activation of T cell proliferation the statement in the reference that Fab fragments of the 9.3 antibody

was ineffective in inducing T cell proliferation is not suggestive of inhibition of proliferation. Read in context Ledbetter et al. teach that the use of a Fab fragment did not result in T cell activation. Given that a Fab fragment when bound to an antigen will inhibit binding of another molecule Ledbetter et al. clearly teaches inhibition of T cell proliferation. Applicant states that since the interaction between CD28 and B7 was not known prior to the date of the claimed invention a suggestion that a Fab fragment would inherently block the interaction between CD28 and B7 represents hindsight reconstruction. To the contrary, a Fab to CD28 will inhibit T cell proliferation due to blocking any ligand, including B7, from binding the CD28 receptor while the Fab is bound. It is not necessary for recognition of the B7 ligand to be known, the Fab will block any CD28 ligand, inherently including B7. This rejection therefore still stands.

32. Claims 35 and 37-40 are rejected under 35 U.S.C. § 102(b) as being anticipated by Damle et al. [J.I. 140(6):1753-1761(1988)]. Damle et al. teach Fab fragments of anti-TP44(CD28) were ineffective in inducing T cell proliferation, see abstract. These antibody Fab fragments will inherently block the interaction between CD28 and B7. The Fab fragment is derived from monoclonal antibody 9.3.

33. No claims allowed.

34. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donald E. Adams whose telephone number is (703) 308-0570. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

April 19, 1995

Donald E. Adams, Ph.D.
Patent Examiner, Group 1800